This Week in The Journal

Role of Locus Coeruleus in Encoding New Contexts

Stephanie L. Grella, Jonathan M. Neil, Hilary T. Edison, Vanessa D. Strong, Irina V. Odintsova, et al.

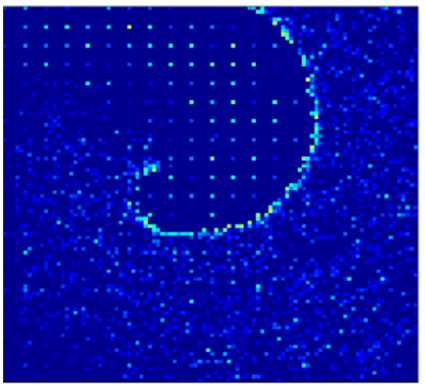
(see pages 445–455)

As rodents explore an enclosure, subsets of hippocampal neurons become active at different locations. The same neuronal ensemble is activated each time an animal traverses an unchanged area, but different ensembles are activated in new environments. These ensembles are thought to form the basis of contextual memories that help animals relocate food sources and safe places.

In real life, however, environments are constantly changing, and similar elements are found in many contexts. Whereas small changes have modest effects on ensemble activity, large changes can induce global remapping of hippocampal representations, with new neurons joining the ensemble, some members becoming active in new locations, and other neurons becoming inactive. What determines whether such global remapping occurs? The locus coeruleus (LC) likely plays a role. LC neurons project to the hippocampus and are activated by novel and salient stimuli. Moreover, inhibiting LC projections to CA3 impairs formation of stable maps when rodents explore novel environments (Wagatsuma et al., 2018 PNAS 115:E310).

Grella et al. tested the role of the LC in hippocampal remapping by allowing rats to explore arenas in two sessions, 30 min apart. To identify neurons activated in each session, the authors examined the subcellular distribution of *Arc* RNA, which increases in the nucleus within minutes of neuronal activation and moves to the cytoplasm ~20 min later. When rats explored the same arena in the first and second sessions, most neurons activated in the first session were reactivated in the second. If the LC was briefly activated before the second session, however, the neuronal populations activated in each session were more distinct. Similar remapping occurred when the second session took place in a novel arena. But when LC was inactivated before the second session, many of the neurons activated in the first session were reactivated in the novel arena. Thus, activating LC induced remapping in familiar environments and inactivating LC prevented remapping in novel environments.

These data support the hypothesis that salient, novel cues promote remapping of hippocampal place fields by activating LC neurons. In addition to allowing animals to distinguish different environments, this remapping might underlie the formation of distinct, episodic memories of salient events that occur in everyday surroundings.



Color map of membrane potential shows the spiral spread of action potentials during seizure-like activity in a network of model neurons. See Jacob et al. for details.

How Synaptic Depression Might Promote Seizures

Theju Jacob, Kyle P. Lillis, Zemin Wang, Waldemar Swiercz, Negah Rahmati, et al.

(see pages 557–575)

People with epilepsy experience recurrent, unprovoked seizures, during which excessive, synchronized neural activity impairs normal function. Between seizures, activity in the epileptic brain appears normal most of the time, but brief (<1 s) bursts of synchronous activity called interictal spikes occur occasionally. Numerous genetic mutations can contribute to the development of epilepsy, and the condition can also emerge after brain trauma, possibly as a result of circuit reorganization. Moreover, seizures can be induced in healthy brains by agents that increase neuronal excitation or decrease inhibition. Nonetheless, what triggers the transition from normal activity to seizure at a given moment in an epileptic brain remains unknown.

Identifying the neural mechanisms underlying seizure onset is difficult because seizures are unpredictable and relatively rare, so activity must be recorded for days or weeks to capture the events. Furthermore, EEG recordings provide insufficient information to discern specific neural mechanisms, and multielectrode arrays record the activity of a limited number of neurons. Therefore, researchers often construct computational models to identify possible mechanisms of seizure genesis.

Jacob et al. sought to create a model that generates both interictal spikes and seizures without requiring changes in input or neuronal parameters. They modeled 100×100 grids of excitatory and inhibitory neurons that integrate synaptic inputs and spike, releasing synaptic vesicles, when a voltage threshold is crossed. Neuronal parameters and connectivity patterns were varied (staying within physiological ranges) to produce epileptiform activity resembling that occurring in biological systems. The authors identified two characteristics that enabled networks to generate interictal spikes and seizures: neurons were densely interconnected with nearby neurons and more sparsely connected with distant neurons; and glutamate release led to vesicle depletion, resulting in short-term synaptic depression followed by gradual recovery. In models with these characteristics, spontaneous activity produced sparse spiking, interictal spikes, or seizures depending on the extent of synaptic depression present in the network when the activity arose.

This work shows that seizure-like activity can, theoretically, arise spontaneously in networks that exhibit activity-dependent synaptic depression, dense local connections, and sparse long-range connections, without the need for changes in excitatory or inhibitory inputs. Future work will need to explore whether such mechanisms contribute to seizures *in vivo*.

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